

# Uterine artery embolization for symptomatic uterine myomas using gelfoam pledgets alone vs. embospheres plus gelfoam pledgets: a randomized comparison

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**Abstract** The aim of the study is to evaluate the feasibility, tolerability, and clinical outcomes of uterine artery embolization (UAE) using gelfoam (G) alone versus embospheres + gelfoam (E + G) in women with symptomatic uterine fibroids. Prospective, patient blinded, randomized controlled pilot study (Level-I). University Affiliated Teaching Hospital. Fifty-nine women with symptomatic uterine fibroids; G ( $n = 31$ ) vs. E + G ( $n = 28$ ). Fluoroscopy-guided trans-femoral artery UAE was performed under intravenous sedation, local anesthesia, and overnight patient-controlled analgesia (PCA) pump using either gelfoam pledgets alone or gelfoam plus embospheres (500–700  $\mu\text{m}$ ). Baseline, 3, 6, and 12 month dominant fibroid and total uterine volume as well as menstrual blood loss and satisfaction scores were compared between the groups. The mean and standard deviation (SD) of uterine volume ( $\text{cm}^3$ ) for G vs G + E at baseline and at 3, 6, and 12 months were 801 (538) vs. 565 (370), 535 (226) vs. 426 (322), 485 (401) vs. 401 (249), and 467 (438) vs. 343 (227), while the mean (SD) of the dominant fibroid volume ( $\text{cm}^3$ ) during the same time periods were 268 (291) vs. 227 (213), 190 (290) vs. 137 (168), 132 (168) vs. 93 (101), and 118 (169) vs. 81 (99), respectively, with no statistical difference (NS) between the two groups at any interval. The corresponding

mean (SD) Rute scores assessing uterine blood loss at the same time periods were 19.2 (6.8) vs. 21.6 (6.1, NS), 11.5 (7.2) vs. 8.1 (5.2, NS), 13.2 (8.3) vs. 6.4 (4.0,  $p < 0.001$ ), and 10.5 (7.9) vs. 5.8 (3.6,  $p < 0.01$ ) for G-alone and E + G, respectively. At 12 months, 71 vs. 79 % of patients were satisfied/very satisfied with their treatment (NS). UAE with gelfoam alone was feasible, tolerable, and equally effective to embospheres + gelfoam in reducing uterine and fibroid volume while it normalized menstrual blood loss.

**Keywords** Fibroids · Myomas · Abnormal uterine bleeding · Uterine artery embolization · Gelfoam · Embospheres

## Introduction

Fibroids affect up to 70 % of women by the age of 50 years [1]. Although some fibroids are asymptomatic and require no treatment, 20–50 % of women will require treatment for menstrual disorders, bulk effects, and/or fertility issues [2]. Following treatment, new fibroids continue to appear and may require additional therapy until menopause with hysterectomy being the most common and effective treatment ([3], Vilos et al. SOGC CPG [4]).

Uterine artery embolization (UAE) using non-absorbable polyvinyl alcohol (PVA) particles was first reported in 1995 [5]. In the last 20 years, this treatment has enjoyed considerable popularity and acceptance particularly among interventional radiologists.

Common occlusion materials include Tris-acryl gelatin microspheres or polyvinyl alcohol particles (PVA) both of which are permanent, non-biodegradable agents. Particle size typically ranges from 500 to 1200  $\mu\text{m}$ .

The mechanism of action of UAE on fibroid death remains speculative. Initially, it was thought that particles entering the

**Precis** At 12 months, UAE with gelfoam alone was equally effective compared with embospheres + gelfoam in reducing uterine and fibroid volume while it normalized menstrual blood loss.

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uterine arteries preferentially flow to, and concentrate within fibroids causing ischemia and fibroid death [5].

Burbank and Hutchins proposed that after uterine artery occlusion (UAO), by any means, both the intra-uterine and myoma vessels occlude by clotting resulting in organ ischemia. The clot formation downstream is the result of stasis at the level of the occluded uterine arteries. Within 6 h, the clots in normal myometrial tissue lyse through the fibrinolytic system, and the uterus reperfuses through collateral broad ligament arteries and survives. Fibroids appear to lack an adequate fibrinolytic system and remain in an extended state of ischemia, resulting in death by the process of necrosis. [6]. The response difference between myometrium and myomas may be due to synergistic effects of vascular density and coagulation/fibrinolysis differences between the two. Evidence for this hypothesis has been summarized [7, 8] and supported by several investigators who have reported equal clinical outcomes of UAE compared with surgical [9] and/or mechanical temporary [7, 8] occlusion of the uterine arteries.

Although UAE with permanent non-biodegradable particles results in good clinical outcomes in the majority of women, these particles are associated with inherent adverse events and complications including excessive peri-UAE pain, misembolization of non-target tissues and organs and, most important, adversely affecting ovarian and reproductive function. On the other hand, it has been shown that uterine artery occlusion (UAO) by surgical means (laparoscopic coagulation, clips, suture ligation, transvaginal occlusion) or using temporary biodegradable material, such as gelfoam, have equal effects on fibroid-related symptoms with less post-UAE pain, no misembolization and possibly no adverse effects on reproduction [7, 8, 10].

We previously reported our initial feasibility study comparing gelfoam alone to gelfoam + embospheres and showed that both methods resulted in equal fibroid and uterine volume reduction at 1 year [11]. We also showed that post-procedure pain may be less in the gelfoam only group. Therefore, the objective of the present study was to compare the two treatments in a randomized group of women by following clinical parameters including total uterine and dominant fibroid volume, menstrual blood loss and patient satisfaction rates at 12 months.

## Materials and methods

This was a pilot prospective, patient blinded, randomized-control, trial (Canadian Task Force Classification I) at a University Affiliated Teaching Hospital. Our objectives were to evaluate the feasibility and clinical outcomes of UAE using gelfoam (G) alone versus gelfoam + embospheres (G + E) in premenopausal women with symptomatic untreated or previously unsuccessfully treated uterine fibroids. Women were

recruited from July 2007 through December 2009 through the primary investigator's (GAV) gynecology clinic. Approval by our institutional review ethics board (HSREB 13849E) and informed consent was obtained from all participants. Women who wished to enhance or preserve their fertility were excluded, as were women with submucosal fibroids, abnormal uterine histopathology, active pelvic inflammatory disease or renal insufficiency (serum creatinine levels >150 mic/L).

Uterine and fibroid volumes ( $\text{cm}^3$ ) were calculated using the formula for the volume of a prolate ellipse [ $\text{length} \times \text{width} \times \text{anterior-posterior diameter} \times (\pi/6)$ ], each measured in cm by transvaginal (TV) ultrasound. There was no upper limit for fibroid diameter or number of fibroids present. All women had normal endometrial biopsy (within 6 months) and Pap smear prior to enrollment.

Randomization to G or G + E was generated by computer randomizing software and all patients were blinded as to the occlusion material they received. The rationale to compare G v G + E was that our local interventional radiologists used routinely G + E for UAE.

**Uterine artery embolization** Two interventional radiologists performed all procedures (RK & GG). Under mild intravenous sedation and local anesthetic, a catheter was introduced through a puncture of the femoral artery under fluoroscopic guidance. The internal iliac artery was catheterized bilaterally with selective 5 French catheter (e.g., Rim, Multipurpose catheter). Contrast was injected to opacify the uterine artery which was then sub selectively catheterized. If there was a large ovarian or vaginal branch opacified, the catheter was advanced distal to the ovarian or vaginal branch.

Micro catheter was used only occasionally, if unable to access more distally the uterine artery with 5 French catheter. If unable to advance the catheter beyond the vaginal or ovarian branch, a micro coil was deposited in the origin of the vaginal or ovarian branch. Contrast was injected again and if there was no major ovarian or vaginal branch opacification, the embolization was carried out at this catheter location. In the gelfoam and particle group of patients, we always used particles first followed by gelfoam and we recorded the volumes used for each patient. We use a sheet of gelfoam which was cut into 1–2 mm cubes and soaked in contrast/saline mixture, then agitated between two syringes to form a gelfoam sludge/slurry. End point for the embolization was visual complete stasis in the uterine artery. Embolization material was added until the uterine arteries were totally occluded bilaterally.

Patients were admitted overnight and were provided with a patient controlled analgesia (PCA) morphine pump and all were discharged home the following morning.

As per usual clinical practice, the uterine and dominant fibroid volumes were measured by transvaginal and

**Table 1** Baseline patient characteristics between gelfoam (G) and gelfoam + embospheres (G + E); age, parity, BMI

	Gelfoam ( <i>n</i> = 31) Mean (SD)	Gelfoam + embosphere ( <i>n</i> = 28) Mean (SD)
Age (yr) <sup>a</sup>	42.0 (6.5)	45.1 (5.3)
Parity <sup>a</sup>	1.4 (1.1)	1.6 (1.2)
BMI (Kg/m <sup>2</sup> ) <sup>a</sup>	27.5 (5.6)	29.0 (7.2)

<sup>a</sup>No statistically significant difference

abdominal ultrasound at baseline and 3, 6, and 12 months post-procedure. Menstrual blood loss (MBL) was assessed by the Aberdeen Menorrhagia Severity Scale (AMSS, Ruta score) at baseline, 3, 6, and 12 months. The Ruta Menorrhagia Severity Scale is a self-administered quality of life instrument comprising 13 questions to assess the patient's menstrual experience from the prior 3 months. A higher score indicates a lower quality of life. This test for menorrhagia has been validated previously for internal reliability and test–retest reliability, as well as being validated against the Short Form-36. [12].

Patient satisfaction rates were assessed at baseline and 12 months by questionnaire. All patients were followed up for the entire 12-month duration.

Mean and standard deviations of fibroid volume, uterine volume, Ruta scores and patient satisfaction rates for both groups were calculated using statistical software (SPSS, IBM Corp, 1 New Orchard Road Armonk, New York, 10,504–1722). Student's *t* test and chi-squared testing was used where appropriate.

## Results

As this was a pilot study, power calculation was not performed. A total of 59 patients were randomized into G (*n* = 31) or G + E (*n* = 28) groups. Patient characteristics of both groups are shown in Table 1. Approximately 90 % of women were Caucasian, 5 % Asian and 5 % of African descent. There was no difference between the groups.

The mean and standard deviation (SD) of total uterine volume (TUV), dominant fibroid volume (DFV) and Ruta scores

of patients randomized to uterine artery embolization using gelfoam alone versus gelfoam + embospheres at baseline and 3, 6, and 12 months are shown in Table 2.

At 12 months, the mean total uterine volume reduction was 42 v. 39 % (NS), (Fig. 1) and the mean reduction in dominant fibroid volume was 56 v. 64 % (NS). (Fig. 2).

At 12 months, the mean reduction of the Ruta score was 45 % (G) vs 73 % (G + E) (*p* < .01) (Fig. 3) and 71 and 79 % of patients were satisfied or very satisfied with the results for G vs G + E, respectively (NS) (Fig. 4).

In the present study, none of our patients reported amenorrhea. Interestingly, women treated with gelfoam alone reported less reduction of menstrual blood loss indicating that their menses were returned to normal rather than experiencing hypomenorrhea.

## Discussion

In general, UAE results in a reduction in fibroid volume of 40 to 60 % and a 50 % mean reduction in blood loss. In a recent meta-analysis, the pooled rates of improvement in menorrhagia, bulk symptoms, and dysmenorrhea at 1 to 2 years of follow-up were 90.1, 82, and 84.4 %, respectively [13]. However, some major adverse events associated with UAE including immediate, post-procedural pain, misembolization and concerns in women wishing to enhance or preserve their fertility have been reported.

**Effects on pain** Most women undergoing UAE experience moderate to severe pain often starting immediately following the procedure and lasting for 2–6 h [11, 14, 15]. Pain immediately following UAE has been well documented and is almost invariably associated with myometrial ischemia. Pron et al. reported a 92 % rate of immediate post-procedural pain following 555 UAE procedures [16].

In the present study, we did not evaluate pain associated with either arm. However, based on evidence from laparoscopic uterine artery occlusion [17] and our own observations with over 120 UAE using gelfoam alone, we propose that gelfoam is associated with less post-procedural pain [11].

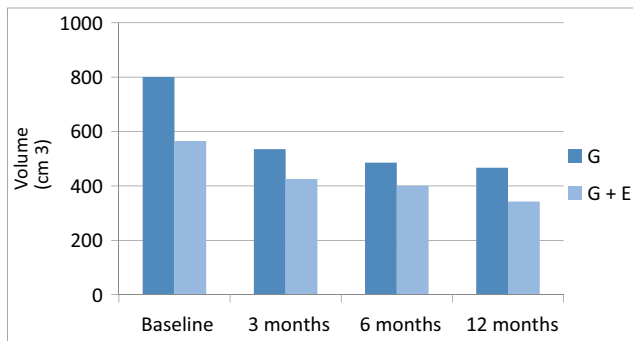
**Table 2** Mean and standard deviation (SD) of total uterine volume (TUV) cm<sup>3</sup>, dominant fibroid volume (DFV) cm<sup>3</sup> and Ruta scores of patients randomized to uterine artery embolization using gelfoam alone (G) versus gelfoam + embospheres (G + E) at baseline and 3, 6, and 12 months

	Baseline	3 months	6 months	12 months
TUV	801 (538) v 565 (370)	535 (226) v 426 (322)	485 (401) v 401 (249)	467 (438) v 343 (227)
DFV	268 (291) v 227 (213)	190 (290) v 137 (168)	132 (168) v 93 (101)	118 (169) v 81 (99)
Ruta	19.2 (6.8) v 21.6 (6.1) <sup>a</sup>	11.5 (7.2) v 8.1 (5.2) <sup>a</sup>	13.2 (8.3) v 6.4 (4.0)*	10.5 (7.9) v 5.8 (3.6)**

Ruta score difference between G and G + E at each time interval

<sup>a</sup>Not significant

\**p* < 0.001, \*\**p* < 0.01

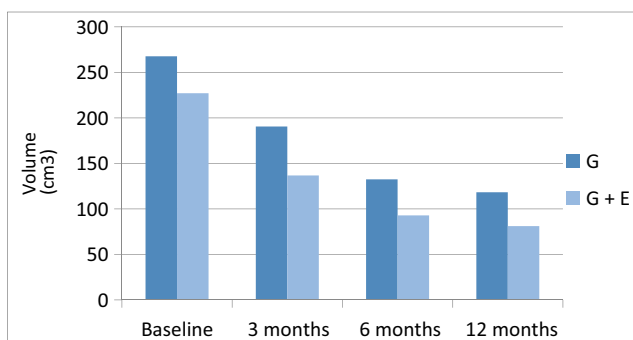


**Fig. 1** Uterine volume (cm<sup>3</sup>) at baseline and post embolization with gelfoam (G) or gelfoam + embospheres (G + E) at 3, 6, and 12 months. Mean reduction at 12 months; 42 % (G) vs. 39 % (G + E) (NS)

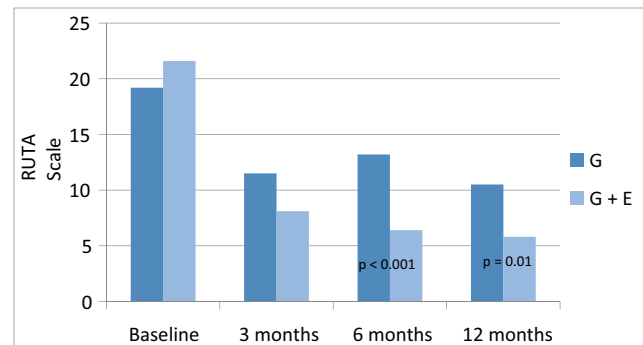
The mechanism involved may be less tissue ischemia because of less migration of gelfoam pledgets to anastomosing vessels.

**Misembolization** During UAE, particles can go anywhere downstream of the arterial injection site and cause ischemic effects on non-target tissues and organs [18]. Although we did not identify any occurrence of misembolization clinically in either group, it is reasonable to speculate that misembolization with gelfoam would be rare because gelfoam pledgets are larger than microspheres. Indeed, in our practice, we have experienced no misembolization, detected angiographically or clinically, in approximately 120 cases and no such complication has been reported in the literature.

**Effects of UAE on the endometrium and AUB** As stated above, UAE results in a 50 % mean reduction in blood loss and the pooled rate of improvement in heavy menstrual bleeding at 1 to 2 years of follow-up was 90.1 % [13]. However, UAE with particles has been associated with transient and permanent amenorrhea [19]. Transient and/or permanent amenorrhea may be one of the reasons that clinical practice guidelines advise caution [3, 20] or even recommend against UAE in women who wish to enhance or retain fertility [21].



**Fig. 2** Fibroid volume (cm<sup>3</sup>) at baseline and post embolization with gelfoam (G) or gelfoam + embospheres (G + E) at 3, 6, and 12 months. Mean reduction at 12 months; 56 % (G) v. 64 % (G + E) (NS)

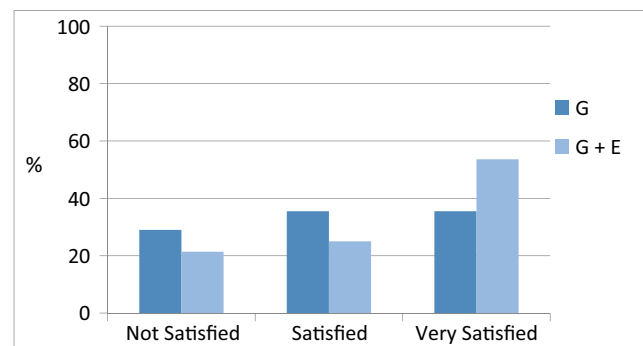


**Fig. 3** Mean Aberdeen Menorrhagia Severity Scale (AMSS, RUTA score) at baseline and post embolization with gelfoam (G) or gelfoam + embospheres (G + E) at 3, 6, and 12 months. Mean reduction at 12 months; 45 % (G) vs 73 % (G + E). Significant at 6 and 12 months

Hysteroscopic and histopathologic evaluation of the endometrial cavity and endometrium following UAE with permanent particles and laparoscopic uterine artery occlusion (LUAO) has been reported indicating that patients who had UAE had a significantly higher incidence of abnormal findings compared with patients treated by LUAO (59.5 vs. 2.7 %,  $p < 0.001$ ). In particular, there was a higher incidence of necrosis in the uterine cavity of patients subjected to UAE (43.2 %) compared with patients after LUAO (2.7 %) ( $p < 0.001$ ) [22]. We did not do hysteroscopic evaluation in any of our patients in the present study.

**Effects of UAE on the ovaries** A major concern regarding UAE is its effects on fertility and pregnancy outcomes [23, 24]. Most if not all of the existing literature on ovarian reserve following UAE has been with permanent particles while the effects of gelfoam remain unknown. However, additional evidence on the efficacy of gelfoam, which provides transient duration of occlusion (7–21 days) and a lesser chance of misembolization, might make gelfoam occlusion a better alternative to particle embolization.

**Efficacy of gelfoam on fibroid related symptoms** The present study, although small, is the first RCT indicating that the



**Fig. 4** Patient satisfaction rates (%) at 12 months post embolization with gelfoam (G) or gelfoam + embospheres (G + E). 71 % (G) v 79 % (G + E) were either satisfied or very satisfied with treatment at 12 months (NS)



clinical outcomes of women treated with UAE using gelfoam alone are similar to those using particles plus gelfoam.

There have been several prospective reports on the efficacy of biodegradable material for UAE. Katsumori et al. followed 96 women for up to 5 years following UAE for fibroids with gelfoam particles. At 5 years, they found symptomatic relief in 89.5 % of women and an overall reintervention rate of 10.5 % [25]. Similar results have been reported in 33 patients embolized with absorbable sponge only. At 12 months, there was a mean reduction in fibroid volume of 61 %, improved menorrhagia in 90 % and decrease of pelvic pain in 78 % of patients. Only one patient required hysterectomy at 21 months for ongoing heavy menstrual bleeding [26].

Selective uterine artery occlusion works by stopping uterine blood flow and inducing clot formation downstream. The concept of temporarily occluding the uterine arteries only has been proposed to contribute to an apoptotic pathway in fibroids which may be all that is needed to accomplish the shrinkage of fibroids seen following embolization with particles [7, 8]. In fact, a study on UAE ( $n = 23$ ) versus LUAO ( $n = 17$ ), reported equal symptom control and myoma volume reduction at 6 months, and fibroid biopsy and immunocytochemical studies demonstrated that fibroids after UAE showed necrosis while after LUAO showed apoptosis [27].

Gelfoam alone may induce a similar apoptotic pathway in fibroids through hypoxia of the tissue rather than complete ischemia noted after UAE with particles which leads to tissue necrosis. Ischemia causes rapid exhaustion of ATP and consumption of glucose, inhibition of apoptosis and induction of necrotic cell death. Cells are characterized by electron-lucent cytoplasm, mitochondrial swelling, loss of plasma membrane integrity and lack of severe damage of nuclei. Cell necrosis occurs in ATP-depleting conditions [28].

In the present study, we compared a commonly used UAE protocol with particles + gelfoam with a theoretically less globally destructive protocol, gelfoam alone. Clinically, all uterine/fibroid volume parameters were equally reduced in both groups (40–60 %) and patient satisfaction rates were equivalent at 12-month follow-up. The reduction in menstrual blood loss at 12 months was significantly improved in both groups; however, it was more so with the combination of gelfoam plus embospheres.

This globally, gentler occlusion technique which focuses on the uterine arteries alone may be why the reduction in Rute scores were significantly greater with the combination of embospheres plus gelfoam as the microparticles can occlude smaller vessels closer to the endometrial basal layers. It is however, important to note that patient satisfaction rates at 1 year were equivalent in both groups regardless of extent of Rute score reduction. Furthermore, the normalization of menstrual blood loss associated with the gelfoam alone rather than extreme reduction associated with UAE with particles may be an added benefit in women who wish to enhance or preserve fertility.

The limitations of our study include that it is a small pilot study performed in a single institution and the differences between groups may disappear with a multicenter study including more participants. The use of ultrasound rather than MRI to assess uterine and fibroid volume may be an additional limitation.

This study has clinical implications. Our review of the evidence indicates that UAO, by any method, is a safe and effective alternative to myomectomy or hysterectomy in women with uterine fibroids. However, the equally effective treatment of symptomatic fibroids by UAO without particles and the serious complications attributed to the particles question the need for particles as agents for blocking the uterine artery blood flow.

We propose a novel concept of selectively occluding the uterine arteries which supply 94 % of all fibroids [29] to induce an alternate biological pathway of self-destruction and reduction in size without leaving permanent material in the uterus and surrounding organs. These biological changes contributed to a significant patient satisfaction rate and improvement of clinical symptoms and may be less damaging to underlying endometrial anatomy. Since gelfoam dissolves within several days, we speculate that this temporary method of occlusion might be a better alternative to permanent UAO, providing additional options such as re-embolizations for new fibroids, preserving/enhancing fertility, allowing better pregnancy outcomes and even considering it as a pre-emptive treatment for small multiple asymptomatic fibroids before they become larger and symptomatic.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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